

**REMARKS**

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections in view of the foregoing amendments and following remarks.

Claims 28, 31, 33, and 39 have been amended to correct typographical errors. Support for the correction of said typographical errors in the claims can be found in paragraphs [0061-0064] of the published application. New claim 58 has been added to claim a particularly preferred embodiment of the invention. No new matter has been added.

**Claim Rejections- 35 U.S.C. § 112**

Claims 28-49 and 53-57 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner asserts that although the specification is enabling for WX-UK1 encapsulated in liposomes containing PC and PG in specific ratios and hemolysis as the side effect, the multitude of compounds fitting the generic derivatives of amidino and guanidine phenylalanine derivatives of the general formula are not enabled. The Examiner states that the instant claim is too broad with respect to the compounds of general formula I, the side effects to be reduced, as well as the generic term 'liposomes' which includes unilamellar, multilamellar, paucilamellar and multivesicular liposomes and the lipids making up these liposomes. To overcome the rejections, claim 28 has been amended and is presently limited to a formulation encapsulated within a phospholipidic liposome that reduces at least one side- effect selected from the group consisting of hemolysis and skin irritation.

Claims 28-49 and 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Specifically, the Examiner indicates that the following language in claim 28, "wherein the active pharmaceutical ingredient comprises a 3-guanidino phenylalanine derivative of general formula I which is effective as a urokinase inhibitor or consists essentially of a 3-amidino phenylalanine derivative" is confusing. The Examiner also asserts that such language is inconsistent with claim 53, depending from claim 28. Applicants submit that claim 28 has been amended to eliminate the confusing language by deleting the phrase "or consists essentially of a 3-amidino phenylalanine derivative of general formula I which is effective as a urokinase inhibitor". Thus, claim 28 is no longer indefinite and is now consistent with claim 53. The Examiner also asserts that it is unclear as to what the unwanted side effects are in claim 28 and that 'such as' in claim 57 is an indefinite term. The subject matter of claim 57, relating to specific unwanted side effects to be reduced, has been incorporated into claim 28 in definite terms and claim 57 has been canceled. Thus, Applicants submit that the rejection is rendered moot and request withdrawal of the outstanding rejection.

#### **Claim Rejections- 35 U.S.C. § 103**

Claims 28-37, 41-48 and 53-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 or DE 10225876.7. Additionally, the Examiner cites the references of Caster (5,776,486), Poiani (5,660,822), and Steck (4,186,183) for encapsulating active agents in a liposome. Applicants submit that none of the cited references or combination of these references renders the present claims obvious without hindsight. The present inventors have discovered very specific formulations for

obtaining the desired effects of the active ingredients while, at the same time, reducing unwanted side effects. Claim 28 has been amended to reflect the specific limitations of this formulation by reciting the specific effective concentration range of the active ingredient in a formulation comprising a phospholipidic liposome, wherein said formulation exhibits reduction of at least one specific unwanted side effect. No combination of the cited art discloses or renders obvious all of the limitations of the presently claimed formulation. Thus, Applicants submit that claim 28 as presently amended overcomes the cited art and is believed to be allowable. In response to the rejection of claims 29-37, 41-48 and 53-57, given that claim 28 is allowable over the cited art, it follows that claims 29-37, 41-48 and 53-57, all depending on claim 28, should also be allowable.

Claims 34-43 and 49 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 by itself or in further combination with Castor, Poiani, and Steck, by themselves or in combination with Barenholz (U.S. 6,156,337). Barenholz discloses adding a solubilizing or dispersing organic solvent to produce freeze-dried liposomes 0.02-5  $\mu\text{m}$  in size (col. 6, line 35). The Examiner asserts that it would have been obvious to use the liposomes taught by Barenholz in the generic liposomes taught by WO 00/04954 to realize the advantages outlined in Barenholz. Barenholz only discloses liposomes comprising DMPC and DMPG in molar ratios of 9:1 (see Example 2). Applicants submit that claims 34-43 and 49 depend from claim 28 and are allowable for at least the reasons above. In addition to the deficiencies of WO 00/04954 and Castor, Poiani, and Steck, the present application recites claims to a PC:DMPG ratio of 70:30, thus distinguishing the present invention from Barenholz and

all other cited references. Thus, Applicants submit that claims 34-43 and 49 are distinguished from the cited references and are believed to be allowable.

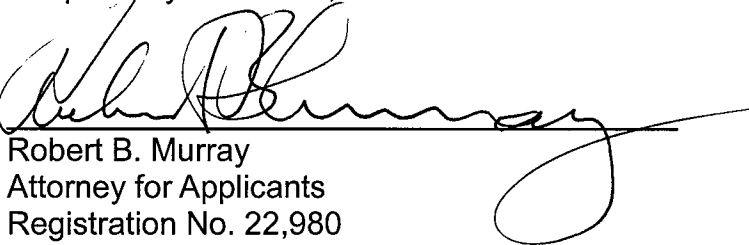
Claim 57 is rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/04954 or DE 102 25 876.7 by themselves or in combination, further with Castor, Poiani, and Steck, by themselves or in combination with Ben-Hur or Kurono for the reasons above combined with the disclosure of Ben-Hur and Kurono regarding reduced hemolysis using liposomes. Claim 57 has been canceled and Applicants submit that the rejection has been rendered moot.

Claim 58 is a new independent claim relating to a method of reducing the unwanted side effects of WX-UK1 and should be allowable for at least the reasoning above and Examiner's comments in the Office Action. Support for this claim is found on page 4, lines 32-33, page 21, lines 27-32, Fig. 2, Table 3, and Example 5.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections. Early and favorable action is awaited.

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